REMARKS

Applicant thanks Supervisory Patent Examiner Hoffman and Examiner Chen for their time and consideration of the present application during the telephonic interview of January 15, 2008 with the undersigned.

During the interview, the Rule 132 Declaration filed July 13, 2007 was discussed. The Examiners were provided with the article included in the appendix of this response, which discusses how to determine if data results in a synergistic effect. Additionally, the particular components and the amount of each component evaluated in the declaration were discussed. It was agreed that filing a response to the Official Action along with the included article would be entered.

Claims 1-5, 7 and 8 remain pending in the application.

Claims 1-4 stand rejected under 35 USC §103(a) as being unpatentable over CHRUBASIK et al. 1998 ("CHRUBASIK"), TAMEJA et al. US 5,629,351 ("TAMEJA"), CHARTERS et al. US 6,541,045 ("CHARTERS"), KEMPER, and LOCKHOFF et al. US 4,710,491 ("LOCKHOFF"). This rejection is respectfully traversed.

CHRUBASIK is offered for teaching anti-inflammatory drugs with salicylic alcohol form Salix species.

TAMEJA is offered for teaching that the gum resin of Boswellia serrata has been used for the treatment of arthritis.

CHARTERS is offered for teaching an anti-inflammatory drug having N-acetyl D-glucosamine.

KEMPER is offered for teaching proanthocyanidin in green tea is effective for treating inflammation.

LOCKHOFF is offered for teaching an anti-arthritic compound having D-glucuronolactone in column 11, line 6.

The position of the Official Action is that because the publications treat inflammation related ailments, which are painful, it would be obvious to combine the ingredients to treat pain.

However, the proposed combination cannot render obvious the claimed invention for at least two reasons:

(I) There is no reason to combine the publications as proposed.

The motivation given for combining the compounds from each publication is to treat pain because the publications treat inflammation related ailments.

However, the compound for which LOCKHOFF is offered, i.e., D-Glucuronolactone, is not used to treat an inflammation related ailment. Rather, LOCKHOFF requires N-glycosylated carboxylic acid derivatives for the treatment of rheumatic diseases.

Indeed, D-glucuronolactone is merely a reactant used to obtain an active compound. A solution is prepared by dissolving D-glucuronolactone in methanol. A mixture of this solution and

sodium methanolate solution is left to stand for a half of an hour. The mixture is neutralized with an acidic ion exchanger, and evaporated to form methyl glucuronate. Methylglucuronate is reacted and worked up to form N-Glucopyranosyl-N-octadecyl-oleic acid amide, which is the active compound used in combating rheumatic diseases according LOCKHOFF. See, e.g., column 11, lines 5-13, Example 15, and column 4, lines 55-59.

Thus, glucuronolactone is not used for the same purposes as the compounds of the other publications, i.e., to treat inflammation related ailments. One of ordinary skill in the art seeking to treat pain would have been discouraged from selecting glucuronolactone, which is merely a reactant required in a multiple step process for obtaining the actual active ingredient.

(II) The proposed combination fails to predict the synergistic effects of the claimed invention.

Even if one were to arbitrarily combine glucuronolactone of LOCKHOFF with the other compounds suggested from the other publications, the combination fails to predict the unexpected results of the claimed composition.

The declaration filed July 13, 2007 shows that the claimed combination of compounds has a synergistic effect. The declaration compares the efficacy of each active compound to the claimed combination of these compounds for treating patients suffering from osteoarthritis of the knee. Efficacy is evaluated

based on the percentage of pain reduction, stiffness reduction, and physical function after 14 days of treatment, e.g., as shown in Tables 1-3 of the declaration.

However, the position of the Official Action is that the declaration shows that the claimed compounds exert an additive effect, not a synergistic effect.

To confirm that the claimed compounds do exert a synergistic effect, the measurements of pain and stiffness from the declaration are analyzed below according to the Bürgi formula, which is a concept that is universally accepted in pharmacology (See Acta Pharmacol Sin 2004 Feb; 25(2): 146-147, in the appendix):

q=observed value/expected value
with a tolerance of ±0.15

where:
q=1 represents simple addition (i.e. additive effect)
q>1 represents synergism or potentiation
q<1 represents antagonism.

The expected value for the data in the declaration is the sum of the individual effects exerted by the single compounds of Group 2, Group 3, Group 4, Group 5 and Group 6, calculated as the difference between Day 0 and Day 14 values in Tables 1 and 2 below:

TABLE 1: Expected Value for Pain

Group	Effect
2	43.6 - 37.3= 6.3
3	43.7 - 37.3 = 4.6
4	43.5 - 41.1 = 2.4
5	45.1 - 42.8 = 2.3
6	44.9 - 44.5 = 0.4
Expected value for Pain	6.3 + 4.6 + 2.4 + 2.3 + 0.4 = **15**

TABLE 2: Expected Value for Stiffness

Group	Effect
2	42.4 - 44.1= -1.7
3	41.9 - 35.3 = 6.7
4	40.3 - 39.1 = 1.2
5	41.2 - 40.8 = 0.4
6	42.7 - 42.5 = 0.2
Expected value for Stiffness	-1.7 + 6.7 + 5.8 + 1.2 + 0.4 + 0.2 = **12.6**

The observed value of the data in the declaration is the effect determined by the composition administered to Group 7 (i.e., the combination of the compounds administered to Groups 2 +3 + 4 +5 + 6), expressed as the difference between Day 0 and Day 14 values in Tables 3 and 4 below:

TABLE 3: Observed Value for Pain (Group 7)
43.8 - 25.3 = **18.5**

TABLE 4: Observed Value for Stiffness (Group 7)
42.8 - 23.2 = **19.6**

The parameter "q" (=observed value/expected value) based on Tables 1-4 above is:

q for Pain: 18.5/15 = **1.23**

q for Stiffness: 19.6/12.6 = **1.55**

As q is greater than 1, the compounds of Groups 2, 3, 4, 5 and 6, i.e., Salix rubra extract, Boswellia serrata exact, Green tea extract, N-acetyl, glucosamine and Glucuronolactone, behave synergistically.

The standard deviation for the results also supports the conclusion the claimed compounds exert a synergist effect. It will be appreciated that the overlapping of the standard deviation values, as pointed out in the Official Action, occurs only for the values referred to Groups 4, 5, and 6 and not for the values referred to as Group 7. That is, the difference between Day 0 and Day 14 in Groups 4, 5, and 6 are not

statistically significant, i.e., each single active compound fails to exert a significant effect on both pain and stiffness in the Day 0 to Day 14 period. On the contrary, in both tests, the response of Group 7 is statistically significant as confirmed by the Table 1 and Table 2 shown above.

Thus, the increased effect observed for Group 7 is clearly attributed to the synergism of the five different active compounds.

A specific issue raised in the Official Action with respect to the declaration is that one of the evaluated active compounds is not claimed, i.e., Boswellia extract "senolee". However, applicant respectfully submits that this is a typographical error, and that the ingredient evaluated in the study is indeed Boswellia extract serrata.

Indeed, the data in the declaration is commensurate in scope with the claimed invention. For example, for a formulation of 600 mg, and according to claim 3, the formulation should contain 200 mg Salix rubra extract and 100 mg of each of Boswellia extract, Green tea extract, N-Acetyl-glucosanine, and Glucuronolactone. The declaration evaluates the efficacy of each individual compound at the appropriate 200 mg or 100 mg and their combination in a 600 mg of the claimed formulation, and, thus, allow one to determine, e.g., by the Bürgi formula, if there is a synergistic effect of the compounds in the claimed formulation.

Thus, in view of the above discussion, the claimed combination results in the unexpected superior results, not predicted by the proposed combination.

Therefore, in view of reasons (I) and (II), the proposed combination cannot render obvious claims 1-4, and withdrawal of the rejection is respectfully requested.

Claims 1-5, 7-8 are rejected under 35 USC §103(a) as being unpatentable over CHRUBASIK, TAMEJA, CHARTERS, KEMPER, and LOCKHOFF, further in view of CHEN et al. US 2002/0032171A1 ("CHEN") and BELCH et al. ("BELCH"). This rejection is respectfully traversed.

CHRUBASIK, TAMEJA, CHARTERS, KEMPER, and LOCKHOFF are offered for the reasons discussed above.

The Official Action recognizes that the proposed combination fails to teach Oenothera biennis oil.

CHEN is offered for teaching triglycerides of Oenothera biennis oil (evening primrose) improves delivery of therapeutic agents.

BELCH is not mentioned *per se*, but it appears that BELCH is offered to teach evening primrose oil in rheumatologic conditions.

However, regardless of the ability of either CHEN or BELCH to teach that for which they are offered, neither can remedy the deficiencies of CHRUBASIK, TAMEJA, CHARTERS, KEMPER, and LOCKHOFF for reference purposes. That is, CHEN and BELCH

fail to suggest using glucuronolactone for the reasons stated in the Official Action, as well as that the claimed combination of active compounds has a synergistic effect as discussed above.

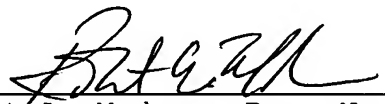
Therefore, claims 1-5 and 7-8 are not rendered obvious, and withdrawal of the rejection is respectfully requested.

In view of the foregoing remarks, entry of the response and allowance of the present application is respectfully requested.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

YOUNG & THOMPSON



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Appendix:

The Appendix includes the following item:

- Acta Pharmacol Sin 2004 Feb; 25(2): 146-147.

Editorial

About the evaluation of drug combination

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The article: "Two useful methods for evaluating antihypertensive drugs in conscious freely moving rats" by Su *et al*[1] represents two aspects of typical advance in pharmacology research methods. The first one is the use of conscious freely moving hypertensive rats in hypotensive drug experiments: it includes the measurement of animal's blood pressure (BP) by intra-arterial catheterization and delivering BP direct data, which are both instantaneous and averageable over a defined time. Needless to say, this method requires a sophistication beyond any usual indirect BP measurement (by tail, for example). Rats, being conscious, preserve their internal reflexes, which, under anesthesia, would be totally or partially inhibited. From this point of view, their BP data, contain much more information than any usual BP measuring method. A real-time BP analysis software should be created in order to make full use of the rich information of the data.

The second aspect is the application of the modified Bürgi formula, whose concept is universally accepted in pharmacology, namely: q=observed value/expected value[2]. If the expected value represents the "addition of drug combination", q=1 would mean simple addition; q>1, synergism or potentiation, q<1, antagonism. However, in practical application, the q never equals exactly 1; so a tolerance of ±0.15 was proposed as an upper and lower limit[3]. The major modification to the formula was the replacement of the original denominator by the Sum of Probability of Independent events: $P_A+P_B-P_A\times P_B$, A and B denoting two independent events. The response percentage would be considered as probability[4].

The "Sum of Probability for Independent Events" is universally recognized[5] in scientific sphere, be it macro- or microscopic. Pharmacologists, especially those show interest in the study of mechanism of action, would like to have mechanism-specific "addition formula". However, in the search of new drugs, the inner mechanism of action is usually unknown. In the pursuit of the best combination, one is interested in the selection of the combination showing the highest efficacy or the least toxicity. The magnitude of the benefit is much less important than the ranking of the combined effects. The mathematical formula is only a tool. As a tool, it will be useful as long as it fulfills the task it is assigned to. From this point of view, the Probablity Sum of Independent Events is useful in terms of sensitivity: the parameter q derived from Bürgi's original idea, provides a good estimation of the ranking. The q parameter thus derived is mechanism-free: it will deliver a true ranking, independent of its mechanism of action. It enjoys a good reproducibility and shows a sound relation with common sense[1,3].

When using this formula, one does not need to change the dose of the drugs involved. In FDA statement about drug combination, the dose of the combined drugs should not be changed. This statement is really noteworthy, for the slope of dose-response curves of every drug is different. Cutting the dose in half, does not imply that the effect is reduced to half of the original effect. Recently, 46 dose-response formulas based on Bliss method have been analyzed (Data kindly provided by Shanghai Bureau of Biological Standardization and Institute of New Drug Toxicology). The end-point was 50 % mortality. Tab 1 showed the new situation (computational issues) at halving the LD_{50}.

To our surprise, only one case of the 46 happened at half of 50 % mortality (25 %). The majority would happen around 5 % (38/46). This mortality distribution table shows clearly the danger of changing the dose of the drugs involved in the combination. The experience of our lab (made during the year 1956-1957)[3] con-

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Tab 1. The relationship between mortality and frequency.

Mortality/%	Frequency
0	2
5	38
10	5
15	0
25	1
30	0
35	0
40	0
45	0
50	0

firmed once again the truth of the table: halving the LD_{50} of the tartar emetic led to a zero mortality, but not 25 % effect as many authors stated. Of course, one would expect a much less steeper slope in the efficacy experiment. However, the mathematical principle remains the same: there is an individual slope for every individual drug. In the combination of two drugs A and B, halving the dose of each drug in the combination would produce a misleading result.

The probability sum formula, using the unchanged dose effect, does not suffer from the drastic and most of time unpredictable variation of the effect. It uses the actual effect of both single groups A and B (the best estimation of single effects).

The design of the experiment being straightforward, is easily carried out, and the computation is within every one's reach. The formula, with its design, is very cost effective.

A final word to say, but not the last, is the optimal choice of the effect level: theoretically, an effect near 40 %–60 % would be adequate, allowing equal opportunity to stimulatory and inhibitory effects. A choice of higher effect level would be good for inhibitory drugs, and vice versa.

Some questions or critics:

1) Drug effects may be related, not independent. The goal being making a rank of different combinations, any method allowing a sound and impartial ordering, may be used. The relation between drugs is difficult to assess, and may be deferred after the ranking. The ranking, per se, is rather mechanism-free.

2) The transformation of quantitative data into quantal data, is rather arbitrary.

Even with an arbitrary line of success or failure, the ranking is not affected, since the same level is applied to each individual datum. Besides, arbitrary judgement is universally accepted even in Olympiads, so long as an equal opportunity and impartiality are practiced. In every special field, only those engaged in the actual animal (or human) experiments are most qualified to define the demarcation line. The demarcation should be based on empirical basis, depending on many variables. A demarcation level, based on researcher's experience, is adequate in absence of any objective demarcation criterion. On the other hand, changing the demarcation level would only change the relative percentage, and not the ranking, which is only an order of placement according to the magnitude of percentages.

3) The parameter q versus the significance test.

Nowadays, scientists, especially biologists, are using significance tests quite frequently. We have compared the Fisher Exact P test with the q, and found that, a significant P (P<0.05), goes far beyond the synergism, and requires a strong potentiation. Therefore, the significance test is not applicable in case of addition. On the other hand, a ranking does not need a significant difference. A minute difference of few milliseconds will make an Olympic champion in free style 100 m swimming, while that difference would be considered as a pure chance, hence not significant at 0.05 level. We therefore conclude that a ranking problem does not need a significance, while a high reproducibility is much more needed. We may repeat the experiment several times. If the ranking remains the same, that would prove the formula enjoys a high reproducibility, which is the case in the article of Su *et al*.

4) The direct measurement of BP in conscious rats, coupled with the modified formula of combination, endowed the article with an attractive progress and efficiency.

REFERENCES

1 Su DF, Xu LP, Miao CY, Xie HH, Shen FM, Jiang YY. Two useful methods for evaluating antihypertensive drugs in conscious freely moving rats. Acta Pharmacol Sin 2004; 25: 148-51.

2 Jin ZJ. Addition in drug combination. Acta Pharmacol Sin 1980; 1: 70-6.

3 Zhang XW, Jin ZJ. The Probability sum and the Isobole in drug combination, a comparison. Advances in pharmacology. Beijing: Chinese Society of Pharmacology; 1982. p 44-56.

4 Jin ZJ. The probability sum method in drug combination. Acta Univ Sec Shanghai 1981; 1: 15-6.

5 Sachs L. Applied statistics. New York: Springer-Verlag; 1982. p 42.